



Meta-analysis in Medicine: Implementation in Hypertension and Renal Disease in Diabetes Mellitus

Yee Hung Choy¹, Anthony Shannon^{2*}

¹ Hong Kong Polytechnic University,
Hung Hom, Kowloon, Hong Kong
E-mail: mayhchoy@inet.polyu.edu.hk

² Warrane College, University of New South Wales
PO Box 123, Kensington, NSW 1465, Australia
E-mail: tony@warrane.unsw.edu.au

* Corresponding author

Received: January 30, 2008

Accepted: April 2, 2008

Published: April 15, 2008

Abstract: This paper utilises meta-analysis and odds ratios to examine the relationship between hypertension and kidney disease in patients with diabetes (Type 1 or Type 2). Significant evidence is found to establish that our quantitative results (overall odds ratios) agree with the qualitative results of the literature, namely that hypertension has a close association with nephropathy and is a major risk factor for this renal disease. The results show that with hypertension diabetic patients have almost 3.5 times the risk of developing nephropathy than those diabetic patients without hypertension.

Keywords: Meta-analysis, Odds ratio, Logit, Chi-square, Case-control studies.

Introduction

Meta-analysis is the process of combining research results in order to strengthen conclusions about therapeutic effectiveness or to plan new studies. Meta-analysis attempts to compare and combine the results of previously published research. Glass [9] was the first to refer to this type of research as “Meta-analysis”. As he said “the term is a bit grand, but it is precise, and apt, and in the spirit of “meta-mathematics”, “meta-psychology”, and “meta-evaluation”. Meta-analysis refers to the analysis of analyses.

There are three other methods of research synthesis, namely, the traditional narrative reviews, the vote counting methods, and the combined significance test methods. Meta-analysis is distinguished from these in the way it uses statistics as we show, and from primary studies (the original analysis of data) and secondary analysis (reanalysis of another's data) by the fact that meta-analyses do not require access to the raw data, but only to summary statistics. Thus the data points for meta-analyses are summary statistics, and a sample of *studies* in meta-analysis is analogous to a sample of *subjects* in primary analysis.

l'Abbé et al. [1] discussed the needs of meta-analysis in clinical research. They pointed out that:

- meta-analysis is a systematic reviewing strategy for addressing research questions that is especially useful when results from several studies disagree with regard to magnitude or direction of effect;



- sample sizes may be individually too small to detect an effect and label it statistically significant;
- large trials may be too costly and time-consuming to perform;
- in evaluating medical treatment and planning new studies, a better understanding is needed of the findings of previous clinical studies. Investigators rely heavily on literature reviews to define the present state of knowledge. Meta-analysis takes a more structured approach to literature review than does traditional narrative review, and this way may be more helpful in evaluating the accumulation of evidence.

In this paper we utilise meta-analysis to combine odds ratios to investigate the connection between hypertension and renal disease in diabetes. This is a major and controversial issue with nondiabetic kidney disease too [9], but we shall not venture there in this paper. Hypertension is defined as high blood pressure, that is, elevation of the arterial blood pressure above the normal range expected in a particular age group. In general, the normal range of blood pressure (sBP/dBP) is around 140/90 mm Hg (the range will change with age) and hypertension may result from kidney disease.

The steps taken in the methodology for the meta-analysis were the standard procedures:

- identification of studies;
- definition of the criteria for the inclusion/exclusion of studies;
- reading, classification, coding, evaluating, and choosing of papers;
- combination of results of the data;
- analysis, interpretation and reporting of results.

We do not go through these standard steps in this paper: the details are available from the authors. What we do, however, is to discuss the statistical context since this is sometimes taken for granted.

Odds ratio

If the probability of an event is p , then the odds of the event are given by

$$\Omega = \frac{p}{1-p}. \quad (1)$$

In other words, odds express the probability that a particular event will occur against the probability that it will not occur. The logarithm of Ω is usually called the log odds or logit:

$$\ln \Omega = \ln \left(\frac{p}{1-p} \right). \quad (2)$$

In clinical research, especially in case-control studies, the odds ratio is commonly used to compare the odds of an event in the treated group with the odds in the control group. In order to illustrate the essence of odds ratio more clearly, let us formulate a 2×2 table which represents the notation for the statistics used to describe unmatched case-control studies.

In Table 1, we notice that the odds in favour of the risk factor's being present in cases is a/c whereas odds in favour of the risk factor's being present in controls is b/d . So the odds ratio is estimated by



$$OR\hat{R} = \hat{\psi} = \frac{a/c}{b/d} = \frac{ad}{bc}. \tag{3}$$

Table 1. Contingency table

	Cases (with disease)	Controls (without disease)
Exposed to risk factor	<i>a</i>	<i>b</i>
Not exposed	<i>c</i>	<i>d</i>
Total	<i>a + c</i>	<i>b + d</i>

In a case-control study, we cannot estimate the risks in each group as we can in a prospective study, since the number of cases and control studies is under the control of the investigator and does not reflect the incidence of the disease in the population. To illustrate this fact let us double both *c* and *d* in Table 1, and so the relative risk would now appear to be $a(c + 2d)/c(a + 2b)$, which in most cases would be different from the previous estimate (that is, $\widehat{RR} = \frac{a/(a + b)}{c/(c + d)}$). Obviously, one

would not expect to change the relative risk simply by increasing the number of controls and so the estimate must be erroneous. Actually, by simply changing the number of controls and/or cases, the relative risk, as described before, could be made to take any value at all! Whereas if the odds ratio is used as a measure of association in case-control studies, there would be no change in the estimate even if we double the number of controls, since we have doubled both the numerator and the denominator of the expression.

Fortunately, if the disease is rare (i.e., $a \ll b, c \ll d$), then the relative risk estimated by

$$RR\hat{R} = \frac{a/(a + b)}{c/(c + d)},$$

which can be rewritten as

$$RR\hat{R} = \frac{a/b}{c/d}.$$

In other words, the relative risks, though they cannot be computed exactly in case-control studies, can be estimated approximately, under special conditions, by the odds ratio.

Estimator of the odds ratio

By referring to Table 1, a consistent estimator of odds ratio (*OR*) in a single study, when all the frequencies in the cells are large, is given by

$$\widehat{OR} = \hat{\psi} = \frac{ad}{bc}. \tag{4}$$

Woolf [15] suggested that if we take the logarithm of \widehat{OR} , such that $\ln(\widehat{OR}) = \ln \hat{\psi} = \ln(ad/bc)$,

$$\tag{5}$$

then in general the sampling distribution of $\ln \hat{\psi}$ is approximately normally distributed about the mean $\ln \psi$ with sampling variance equals to

$$SE^2(\ln(\hat{\psi})) = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}. \quad (6)$$

Hence we can find the $100(1-\alpha)\%$ confidence interval for $\ln \psi$ by calculating the confidence limits

$$\ln \hat{\psi} \pm [z_{\alpha/2} \times SE(\ln \hat{\psi})]. \quad (7)$$

The confidence limits for the population of *OR* is then obtained by exponentiating Eq. (7) to give $\exp(\ln \hat{\psi} \pm [z_{\alpha/2} \times SE(\ln \hat{\psi})])$. (8)

The limitation of Woolf's method (also known as the logit method) is that any of the numbers *a*, *b*, *c* or *d* should not be too small. The variance may even be non-defined if any one of them is equal to zero.

Combined estimate of the log odds ratios across studies

Suppose there are *k* studies to be meta-analyzed. Let n_{i1} and n_{i2} be the sample sizes in the *i*-th studies, and let p_{i1} and p_{i2} be the proportion having the characteristic under study. Thus for instance in a randomized controlled trial the two groups would be the treated and placebo samples and the characteristic under study may be relapse or some other kind of failure. In an epidemiological case-control study the two groups would be cases and controls and the characteristic under study would be exposure to the hypothesized risk factor.

Breslow and Day [4] suggested that a full analysis of such a series of 2×2 tables (like Table 1) should comprise

- a test of full hypothesis that $\psi = 1$ in all tables (that is, $\psi = 1$ for all the *k* studies involved);
- point and interval estimation of ψ assumed to be common to all tables; and
- a test of the homogeneity that ψ is constant across tables;

There are at least two kinds of estimators which we are going to discuss.

Logit estimate of the common odds ratio

The logarithm of the estimate of odds ratio in studies *i*, denoted by $\ln \hat{\psi}_i$ is equal to

$$\ln \hat{\psi}_i = \ln \left(\frac{p_{i1}(1-p_{i2})}{p_{i2}(1-p_{i1})} \right) \quad (9)$$

and the standard error of $\ln \hat{\psi}_i$ is given by

$$SE(\ln \hat{\psi}_i) = \ln \left(\frac{1}{n_{i1}(1-p_{i1})} + \frac{1}{n_{i2}(1-p_{i2})} \right). \quad (10)$$



In fact it can be easily shown that the expressions in Eq. (5) and Eq. (9) are equal, as are those in Eqs. (6) and (10) for general i . The weights w_i assigned to the particular $\ln \hat{\psi}_i$ are given by

$$w_i = \frac{1}{\text{var}(\ln(\hat{\psi}_i))} . \tag{11}$$

In doing this Woolf [12] stated that the overall $\ln \hat{\psi}_w$ is given by

$$\ln \hat{\psi}_w = \frac{\sum_{i=1}^k w_i \ln \hat{\psi}_i}{\sum_{i=1}^k w_i} ,$$

that is,

$$\ln \hat{\psi}_i = \frac{\sum_{i=1}^k w_i \left(\frac{a_i d_i}{b_i c_i} \right)}{\sum_{i=1}^k w_i} ,$$

where

$$w_i = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i} .$$

The variance of the overall estimate $\ln \hat{\psi}_w$ is given by the reciprocal of the sum of the weights, namely

$$\text{var}(\ln \hat{\psi}_w) = \left(\sum w_i \right)^{-1} .$$

Having defined the overall estimate $\ln \hat{\psi}_w$, we can then construct the 95% confidence interval for the parameter $\ln \psi$ as follows:

$$\ln \hat{\psi}_w - 1.96 \sqrt{\sum w_i} \leq \ln \psi \leq \ln \hat{\psi}_w + 1.96 \sqrt{\sum w_i} .$$

The limitation of the logit combined estimate is that if any of the entries in a given table is zero, the log odds ratio and weight for that table will be non-defined. The usual remedy for this problem is to add 1/2 to each entry before calculating the individual odds ratios and weights. However, the estimate calculated in this way is subject to unacceptable bias when combining information from large numbers of strata, each containing only a few cases or controls. It is not recommended for general use [4]. A more acceptable estimate is the famous Mantel-Haenszel estimate [10].

Mantel-Haenszel estimate

Mantel and Haenszel proposed as a summary relative risk estimate the statistic

$$\hat{\psi}_{MH} = \frac{\sum_{i=1}^k a_i d_i / N_i}{\sum_{i=1}^k b_i c_i / N_i} , \tag{12}$$

where

$$N_i = a_i + b_i + c_i + d_i.$$

This estimate can be recognized as a weighted average of the individual odds ratios

$$\hat{\psi}_i = \frac{a_i d_i}{b_i c_i}$$

with weights $w_i = b_i c_i / N_i$ which approximate the inverse variances of the individual estimates when ψ is near 1. The advantage of using the Mantel-Haenszel formula as described by Eq. (12) is that the formula is not affected by zero cell entries and gives a consistent estimate of the common odds ratio even with large numbers of small strata. When the data in each stratum are more extensive it yields results which are in good agreement with the maximum likelihood estimators [7].

Mantel and Haenszel also gave a significance test of the hypothesis that $\psi = 1$. For instance, if there were no association between the risk factor and the disease, the expected value and the variance of a_i in the 2×2 tables will be given by

$$E(a_i) = \frac{(a_i + b_i)(c_i + d_i)}{n_i}$$
$$\text{var}(a_i) = \frac{(a_i + b_i)(c_i + d_i)(a_i + c_i)(b_i + d_i)}{n_i^2(n_i - 1)}$$

The test is calculated by adding the differences between the observed and expected values of a_i over the subsets. Since these subsets are independent, the variance of the sum of the differences is equal to the sum of the separate variances. This gives as a test statistic

$$X_{MH}^2 = \frac{[\sum a_i - \sum E(a_i)]^2}{\sum \text{var}(a_i)}$$

which is approximately $X_{(1)}^2$.

In order to construct the confidence interval, Miettinen [9] suggested that if the variance of $\hat{\psi}_{MH}$ were known, then, under normal theory, a test statistic of the hypothesis $\psi = 1$ ($\ln \psi = 0$) would be $z = \ln(\hat{\psi}_{MH}) / SE(\hat{\psi}_{MH})$. (13)

taken as an approximate standardized normal deviate. The test statistic X_{MH}^2 is approximately $X_{(1)}^2$ and taking the square root gives an approximate standardized normal deviate. Hence we can let $z = X_{MH}$, and upon substituting into Eq. (13) we get

$$SE(\ln \hat{\psi}_{MH}) = (\ln \hat{\psi}_{MH}) / X_{MH}.$$

Hence the 95% confidence limits for $\ln \psi$ can be constructed as follows:

$$\ln \hat{\psi}_{MH} \pm 1.96 \ln \hat{\psi}_{MH} / X_{MH}$$

from the anti-logarithm, the 95% confidence limit or ψ will be given by

$$\exp((\ln \hat{\psi}_{MH}) [1 \pm 1.96 / X_{MH}]) = \hat{\psi}_{MH}^{[1 \pm 1.96 / X_{MH}]}$$

Homogeneity of odds ratios across studies

In order to test for homogeneity, we can use the logit approach, that is, take the weighted sum of the square deviations between the separate estimates of log odds ratio in each 2x2 table and the overall log estimate $\ln \hat{\psi}_w$ obtained by the logit method. Thus let

$$Q_2 = \sum w_i (\ln \hat{\psi}_i - \ln \hat{\psi}_w)^2,$$

where

$$\ln \hat{\psi}_w = \frac{\sum w_i \ln \hat{\psi}_i}{\sum w_i}.$$

If all the k studies have the same population odds ratio, then the test statistic Q_2 has an asymptotic chi-square distribution given by

$$Q_2 \approx X_{k-1}^2.$$

If the null hypothesis is not rejected, then we can combine the $(\ln \hat{\psi}_i)$'s together across the k studies and obtain the overall estimate $\ln \hat{\psi}_w$.

Nevertheless, much of the literature was not amenable to combination of quantitative results even when the conclusions could be compared qualitatively because they lacked adequate controls or they were a mixture of longitudinal and cross-sectional designs or they were isolated studies with small sample sizes. The data which are appropriate for comparison quantitatively by meta-analysis are shown in Table 2. Five studies were used for comparison from Table 3 where we found that study 1, study 5 showed a “significant” association between nephropathy and hypertension (Fig. 1).

Table 2. Studies in hypertension as a risk factor for diabetic nephropathy

Study No	Study name	Year of study	Nephropathy		Without nephropathy	
			With hypertension	Without hypertension	With hypertension	Without hypertension
1	Barzilay	1992	28	18	17	61
2	Earle	1992	13	48	9	52
3	Gall	1997	22	19	51	84
4	Nelson	1996	12	72	1	19
5	Rossing	1996	107	58	108	485

The overall odds ratio is 3.5617 which implies that the diabetic patients with hypertension are approximately 3.5 times as likely to progress diabetic nephropathy as those without hypertension. The 95% confidence interval for the overall odds ratio indicates that, in patients similar to the ones studied, the true odds ratio is somewhere between 1.6159 and 7.8508. There is a strong evidence that hypertension is highly associated with the development of nephropathy because there is a large

overall combined chi-square and a small corresponding p -value ($X^2 = 136.1292, p < 0.000001$).

This shows a statistically significant result of a close relation between hypertension and nephropathy.

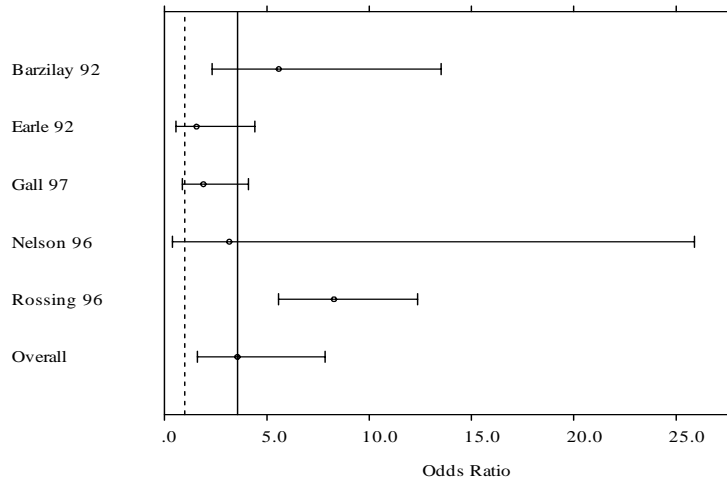


Fig. 1 Hypertension as a risk factor for diabetes

Table 3. Odds ratio and 95% CI for nephropathy among hypertension study groups

Study No.	Study name	Odds ratio	95% confidence interval	
1	Barzilay [3]	5.5817	2.3366	13.5137
2	Earle [5]	1.5648	0.5610	4.4154
3	Gall [6]	1.9071	0.8896	4.0998
4	Nelson [12]	3.1667	0.3818	25.9034
5	Rossing [14]	8.2846	5.5592	12.3650
Overall		3.5617	1.6159	7.8508
Overall combined Chi-square = 136.1292, df = 1, $p < 0.000001$				

Conclusion

There is compelling evidence that the quantitative results (overall odds ratios) in this paper agree with the qualitative results of the literature, namely that hypertension has a close association with nephropathy and is a major risk factor for this disease. This conclusion is in accord with other recent research on diabetic patients [2] and more generally [13]. The results further show that with hypertension diabetic patients have almost 3.5 times the risk of developing nephropathy than those diabetic patients without hypertension.



References

1. l'Abbe K. A., A. S. Detsky, K. O'Rourke (1987). Meta-analysis in Clinical Research, *Annals of Internal Medicine*, 107, 224-233.
2. Abbott K., E. Basta, G. L. Bakris (2004). Blood Pressure Control and Nephroprotection in Diabetes, *Journal of Clinical Pharmacology*, 44, 431-438.
3. Barzilay J., J. H. Warram, M. Bak, L. M. B. Laffel, M. Canessa, A. S. Krolewski (1992). Risk Factor for Nephropathy and Hypertension in IDDM, *Kidney International*, 41, 723-730.
4. Breslow N. E., N. E. Day (1980). *Statistical Methods in Cancer Research – The Analysis of Case-control Studies*, Volume I. Lyon: International Agency for Research on Cancer.
5. Earle K., J. Walker, C. Hill, G. Viberti (1992). Familial Clustering of Cardio-vascular Disease in Patients with Insulin-dependent Diabetes and Nephropathy, *The New England Journal of Medicine*, 326, 673-677.
6. Gall M-A., P. Hougaard, K. Borch-Johnsen, H-H. Parving (1997). Risk Factors for the Development of the Incipient and Overt Diabetic and Overt Diabetic Nephropathy in Patients with NIDDM: Prospective, Observational Study, *British Medical Journal*, 314, 783-788.
7. Gart J. J. (1971). The Comparison of Proportions: A Review of Significance Tests, Confidence Intervals, and Adjustments for Stratification, *Review of the International Statistical Institute*, 39, 148-169.
8. Glass G. V. (1976). Primary, Secondary, and Meta-analysis of Research, *Educational Researcher*, 5(10), 3-8.
9. Kida Y. (2005). Target Blood Pressure and Kidney Disease, *Annals of Internal Medicine*. 143, 310-311.
10. Mantel N., W. Haenszel (1959). Statistical Aspects of the Analysis of Data from Retrospective Studies of Disease, *Journal of the National Cancer Institute*, 22, 719-711.
11. Miettinen O. S. (1976). Estimability and Estimation in Case-referent Studies, *American Journal of Epidemiology*, 103, 226-235.
12. Nelson R. G., P. H. Bennett, G. J. Beck, M. Tan, W. C. Knowler, W. E. Mitch, G. H. Hirschman, B. D. Myers (1996). Development and Progression of Renal Disease in Pima Indians with NIDDM, *The New England Journal of Medicine*, 335, 1636-1642.
13. Ravera M., M. Re, L. Deferrari, S. Vettoretti, G. Deferrari (2006). Importance of Blood Pressure Control in Chronic Kidney Disease, *Journal of the American Society of Nephrology*, 17, 98-103.
14. Rossing P., P. Hougaard, K. Borch-Johnsen, H-H. Parving (1996). Predictors of Mortality in Insulin-dependent Diabetes: 10 Year Observational Follow up Study, *British Medical Journal*, 313, 779-784.
15. Woolf B. (1955). On Estimating the Relation between Blood Group and Disease, *Annals of Human Genetics*, 19, 251-253.



Yee Hung (Edward) Choy, Ph.D.

E-mail: mayhchoy@inet.polyu.edu.hk



Dr. Yee Hung (Edward) Choy is an Assistant Professor of the Department of Applied Mathematics, Hong Kong Polytechnic University. He has taught various subjects in Mathematics and Statistics to different levels of students, ranging from Associated degree up to Master levels.

He holds the degrees of M.Sc. and Ph.D. and is also a Chartered Statistician of the Royal Statistical Society of United Kingdom. His research interests are in Medical Statistics, epidemiology, particularly through the application of Meta-analysis. He is the principal investigator of several projects funded by the research grants of the Department. He has also provided various kinds of consultancy commissioned by the government or public bodies.

He enjoys reading, hiking, theatre, watching soccer matches, and history.

Anthony G. (Tony) Shannon, Prof., Ph.D., Ed.D., D.Sc.

E-mail: tony@warrane.unsw.edu.au



Professor A. G. (Tony) Shannon AM is an Emeritus Professor of the University of Technology, Sydney, where he was Foundation Dean of the University Graduate School and Professor of Applied Mathematics, and where he is currently Chair of the Key University Research Centre for Health Technologies.

He holds the degrees of Ph.D., Ed.D. and D.Sc. He is co-author of numerous books and articles in medicine, mathematics and education. His research interests are in the philosophy of education and epidemiology, particularly through the application of generalized nets and intuitionistic fuzzy logic. He has taught and mentored at all levels from primary school to post-doctoral.

Prof. Shannon is a Fellow of several professional societies and a member of several course advisory committees at private higher education providers. He is on the Board of Trustees of Champion College, a liberal arts degree granting institution in Sydney. In June 1987 he was appointed a Member of the Order of Australia for services to education.

He enjoys reading, walking, theatre, number theory, and thoroughbred racing.